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Tenecteplase vs Alteplase for Patients With Acute Ischemic Stroke
The ORIGINAL Randomized Clinical Trial

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IMPORTANCE Tenecteplase is a bioengineered variant of alteplase with greater fibrin specificity and a longer half-life, allowing single-bolus administration. Evidence on the treatment effect of tenecteplase 0.25 mg/kg in Chinese patients with acute ischemic stroke (AIS) is limited.

OBJECTIVE To establish the noninferiority of tenecteplase to alteplase in patients with AIS within 4.5 hours of symptom onset.

DESIGN, SETTING, AND PARTICIPANTS The ORIGINAL study was a multicenter, active-controlled, parallel-group, randomized, open-label, blinded end point, noninferiority trial conducted between July 14, 2021, and July 14, 2023. Participants were recruited from 55 neurology clinics and stroke centers in China and were eligible if they had AIS with a National Institutes of Health Stroke Scale score of 1 to 25 with measurable neurologic deficit and were symptomatic for at least 30 minutes without significant improvement.

INTERVENTIONS Patients were randomized (1:1) within 4.5 hours of symptom onset to receive intravenous tenecteplase (0.25 mg/kg) or intravenous alteplase (0.9 mg/kg).

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients with a modified Rankin Scale (mRS) score of 0 or 1 (no symptoms or no significant disability) at day 90, tested for noninferiority (risk ratio [RR] margin, 0.937). Safety end points included symptomatic intracerebral hemorrhage (per European Cooperative Acute Stroke Study III definition) and 90-day all-cause mortality.

RESULTS Among the 1489 patients randomized, 1465 patients were included in the full analysis set (732 in the tenecteplase group; 733 in the alteplase group) and 446 (30.4%) were female. The primary outcome occurred in 72.7% (532/732) of patients receiving tenecteplase and 70.3% (515/733) receiving alteplase (RR, 1.03 [95% CI, 0.97-1.09]; noninferiority threshold met). Symptomatic intracerebral hemorrhage occurred in 9 patients (1.2%) in each group (RR, 1.01 [95% CI, 0.37-2.70]). The 90-day mortality rate was 4.6% (34/732) in the tenecteplase group and 5.8% (43/736) in the alteplase group (RR, 0.80 [95% CI, 0.51-1.23]).

CONCLUSIONS AND RELEVANCE In patients with AIS eligible for intravenous thrombolysis within 4.5 hours after stroke onset, tenecteplase was noninferior to alteplase with respect to excellent functional outcome (mRS score of 0 or 1) at 90 days and had a similar safety profile. Findings from this study support tenecteplase as a suitable alternative to alteplase in this setting.

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Visual Abstract

Supplemental content

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The burden of stroke continues to increase worldwide.[1,2] Although stroke is the third leading cause of death and disability globally,[1] it remains the leading cause in China.[3] Adults in China have the highest lifetime risk of stroke worldwide,[1] including ischemic stroke, which represents the majority of all strokes.[1] Alteplase, administered as a bolus followed by a 1-hour infusion, is the standard of care for eligible individuals within 4.5 hours of onset of acute ischemic stroke (AIS),[4-6] and is currently the main thrombolytic agent licensed for use in these individuals.[7,8]

Tenecteplase is a bioengineered variant of the tissue plasminogen activator alteplase, whereby the alteplase protein structure is modified at 3 sites (T103N, N117Q, KHRR 296-299 AAAA), resulting in a higher fibrin specificity and a longer half-life, allowing administration as a single intravenous bolus.[9,10] Tenecteplase is globally licensed as a first-line thrombolytic agent for patients with acute ST-segment elevation myocardial infarction when coronary intervention cannot be performed in a timely manner,[7,8] based on similar efficacy and a reduced rate of systemic bleeding compared with alteplase.[11] In patients with AIS, there is a growing body of evidence from investigator-initiated trials showing comparable rates of excellent functional outcomes at 90 days, mortality, and symptomatic intracerebral hemorrhage (sICH) between tenecteplase and alteplase.[12-16] These findings support the inclusion of tenecteplase as a treatment option for eligible patients with AIS in international guidelines.[4-6] However, evidence on the treatment effect of tenecteplase 0.25 mg/kg in Chinese patients with AIS is limited.

The phase 3 ORIGINAL study aimed to assess the noninferiority of tenecteplase to alteplase (both manufactured by Boehringer Ingelheim) in Chinese patients with AIS within 4.5 hours of symptom onset.

Key Points

Question Is tenecteplase noninferior to alteplase for patients with acute ischemic stroke (AIS) eligible for intravenous thrombolysis within 4.5 hours after stroke onset?

Findings In this noninferiority randomized clinical trial including 1489 participants, a total of 72.7% of patients receiving tenecteplase and 70.3% receiving alteplase achieved modified Rankin Scale scores of 0 or 1 (excellent functional outcome), resulting in a risk ratio of 1.03 (95% CI, 0.97-1.09), which met the predefined noninferiority margin of 0.937.

Meaning Findings from this study support tenecteplase as a suitable alternative to alteplase for patients with AIS eligible for thrombolysis.

Methods

Study Design

ORIGINAL was a multicenter, active-controlled, parallel-group, randomized, open-label, blinded end point, phase 3 noninferiority study conducted across 55 neurology clinics and/or stroke centers in China. A full list of study investigators and sites is provided in eAppendix 1 in Supplement 1. The duration of the ORIGINAL study overlapped with another ongoing trial[17] in China; it was ensured that concurrent recruitment did not occur in sites that participated in both trials. Prior to enrollment, all participants (or their legally accepted representatives) provided written informed consent in accordance with good clinical practice and local legislation. An impartial witness could be called upon to attest to the consent process if the participant could not read.

The study protocol was approved by the appropriate institutional review board or independent ethics committee at each study site and by all relevant competent authorities. The study was conducted in compliance with the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol has been published elsewhere[18] and is available in Supplement 2.

Patients

Chinese adults (aged ≥18 years) were eligible for enrollment if they had an AIS with a National Institutes of Health Stroke Scale (NIHSS) score of 1 to 25, had measurable neurologic deficit, had been symptomatic for at least 30 minutes without significant improvement, and were able to receive thrombolytic therapy within 4.5 hours of symptom onset. Individuals with an NIHSS score of less than 4 were required to have a measurable deficit in motor function score for the arms or legs of at least 1. Individuals in whom endovascular thrombectomy was planned were eligible. Noncontrast computed tomography was used at screening to exclude patients presenting with intracranial hemorrhage. A list of exclusion criteria is provided in Supplement 1.

Randomization and Masking

Eligible patients were randomly assigned (1:1) to receive either intravenous tenecteplase or intravenous alteplase. Randomization was performed using a centralized, web-based, real-time interactive response technology system. Randomization was stratified by baseline NIHSS score (<6, 6-15, >15) and age (≤80, >80 years), and a randomization sequence with a block size of 4 was generated using a valid system involving a pseudorandom number generator. Study drugs were given open label and outcome assessments were blinded.

Procedures

Patients received either intravenous tenecteplase (Boehringer Ingelheim, 0.25 mg/kg; maximum dose, 25 mg) administered as a bolus over 5 to 10 seconds or intravenous alteplase (Boehringer Ingelheim, 0.9 mg/kg; maximum dose, 90 mg) with 10% of the dose administered as an initial bolus and the remainder administered immediately as an infusion over 1 hour. Treatment was administered within 4.5 hours of the onset of ischemic stroke symptoms.

Modified Rankin Scale (mRS) score was assessed at 1 month and 3 months by certified neurologists who were competent in using the mRS in their clinical practice. The mRS score assessors received additional training and were authorized in the

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usage of the mRS before each site initiation.[19] NIHSS measurements were taken at 2 hours, 24 hours, 1 week, 1 month, and 3 months; Barthel Index score at 1 month and 3 months; and the Glasgow Outcome Scale score at 3 months. With the exception of the 2-hour NIHSS score, all clinical assessments were performed by assessors who were blinded to treatment assignment and independent of those who enrolled patients and administered treatments. Noncontrast computed tomography scans were taken at 22 to 36 hours after initiating the study drug to identify any intracranial hemorrhage.

An independent end point adjudication committee, which comprised specialists with proven relevant expertise, adjudicated all sICH events on an ongoing basis. The end point adjudication committee was blinded at all end point and clinical assessments. An independent data monitoring committee monitored critical safety events and reviewed unblinded safety data based on the results of the end point adjudication committee review. The data monitoring committee also monitored the progress of the study, focusing on safety outcomes, and performed regular benefit-risk assessments, the results of which guided their advice regarding the continuation or termination of the study. Both committees were fully external and independent of the study investigators, sites, and sponsor. Detailed statistical analyses are described in the statistical analysis plan (Supplement 3).

Outcomes

The primary outcome was the proportion of patients who achieved an mRS score of 0 (no symptoms at all) or 1 (no significant disability despite symptoms; able to carry out all usual duties and activities) on day 90. Secondary efficacy outcomes were major neurologic improvement at 24 hours (NIHSS score of 0 or at least a 4-point improvement from baseline) and the following outcomes on day 90: mRS score of 0 to 2, change in NIHSS score from baseline, distribution of mRS scores (mRS scores range from 0-6), and a Barthel Index score of at least 95. Secondary safety outcomes were sICH while receiving treatment (up to 36 hours after the end of study drug administration) based on the European Cooperative Acute Stroke Study (ECASS) III definition,[20] all-cause mortality within 90 days, and an mRS score of 5 (severe disability) or 6 (death) on day 90.

Further functional outcomes and safety end points are listed in Supplement 1 and include sICH per the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) and ECASS II definitions and the frequency and severity of adverse events.

Statistical Analysis

A sample size of 1478 patients (approximately 739 per treatment group) would provide 80% power to demonstrate noninferiority between tenecteplase and alteplase in terms of the proportion of patients who achieved an mRS score of 0 or 1 on day 90 (primary outcome), using a noninferiority risk ratio (RR) margin of 0.937 and a type I error rate of .025 (1-sided) and based on an expected response rate of 63% with alteplase[21,22] and a conservative estimate of 65.8% for tenecteplase.[15] The noninferiority margin was initially designated as a −9.5% absolute difference based on the PROST study,[23] which used a margin of 10%. This was revised to −5% following the release of the AcT trial,[15] although this margin was not implemented. In alignment with suggestions from the China Center for Drug Evaluation, the calculation of the noninferiority margin was revised to be based on an RR and f (ie, fraction of the preserved alteplase treatment effect by tenecteplase) at or above 0.5.[24] According to results of a meta-analysis of data from randomized trials with intravenous alteplase in AIS, the unadjusted RR for achieving an mRS score of 0 or 1 vs placebo was 1.24 (95% CI, 1.14-1.36).[25] By considering the lower bound of 1.14 as M1 and f = 0.5, M2 was then calculated as 1.0677.[24] Therefore, the noninferiority margin (1/M2) for RR was set as 0.937. This RR boundary of 0.937 would correspond to a −3.97% risk difference between tenecteplase and alteplase, assuming an expected response rate of 63% with alteplase. Superiority for the primary outcome was tested in a hierarchical manner (ie, upon demonstration first of noninferiority). The analysis of the primary outcome was undertaken using a log-binomial regression model adjusted for continuous covariates (baseline NIHSS score, age, and time to drug administration since the onset of AIS) and transformed into an RR with respective 95% CI based on the full analysis set (all patients who were randomly assigned to and received any dose of the study drug; data were analyzed according to the randomized treatment groups). The multiple imputation approach was used to handle missing data of primary outcome.

Sensitivity analyses of the primary outcome were performed in the full analysis set with the last observation carried forward method to impute missing data for surviving patients and observed cases approach. The primary outcome was also analyzed in the following predefined subgroups: baseline NIHSS score (<6, 6-15, >15, and <4, ≥4), age (≤80, >80 years), time to drug administration (≤3, >3 hours), sex (male, female), atrial fibrillation (yes, no), diabetes (yes, no), and thrombectomy performed (yes, no). The log-binomial model was fitted to each subgroup separately by modeling the primary outcome with treatment, subgroup, and treatment by subgroup interaction terms and the multiple imputation approach was used for missing data. For patients who underwent computed tomography angiography (CTA) or magnetic resonance angiography (MRA) at baseline at their physician's discretion, an exploratory post hoc analysis of the primary outcome was performed according to subgroups of whether occlusions were detected. Supplemental analyses of the primary end point were also performed on the per-protocol set (patients included in the full analysis set, but who did not have any important protocol deviations that may affect the evaluation of the primary end point). Further information regarding sensitivity and supplemental analyses is described in Supplement 1. A post hoc analysis was performed using the generalized estimating equations Poisson regression model, with robust standard error to account for clustering (ie, study site).[26]

Analyses of secondary and further outcomes were exploratory, conducted using a superiority framework and reporting 2-sided 95% CIs. A similar model adopted in the analysis of the primary outcome was used for the secondary efficacy functional outcomes. For the continuous end point

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of change from baseline NIHSS score at day 90, the mixed model repeated measures approach was employed. The proportion of patients with adjudicated sICH per the ECASS III definition and all-cause mortality within 90 days while receiving treatment was analyzed in the safety set (all patients who were randomly assigned to and received study drug; data were analyzed according to treatment received) using the Suissa-Shuster test and χ^2 test, respectively. The proportion of patients with an mRS score of 5 or 6 on day 90 was analyzed using the log-binomial regression model adjusted for continuous covariates in the full analysis set. In this set, a descriptive analysis was also performed for the distribution of mRS at day 90 end point.

If the log-binomial regression model failed to converge, a modified Poisson regression model would be used. For analyses of functional outcomes, data missing due to death were replaced as the worst values (ie, 6 for mRS score, 42 for NIHSS score, 0 for the Barthel Index score, and 5 for the Glasgow Outcome Scale score).

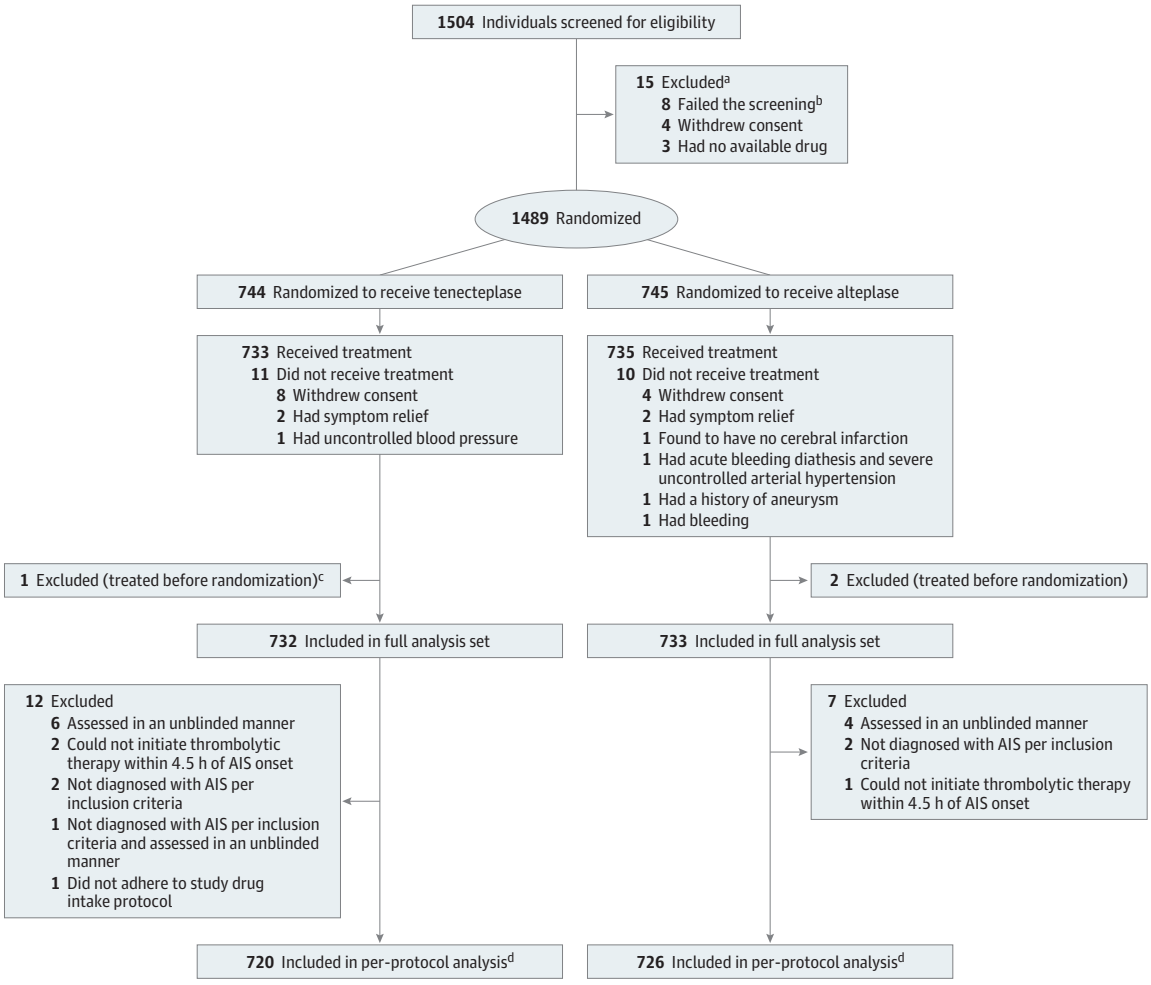
All statistical analyses were performed using SAS version 9.4 (SAS Institute). This study followed the CONSORT guideline for reporting of randomized clinical trials.

Results

Study Population

Between July 14, 2021, and July 14, 2023, 1504 patients were screened across 55 sites in China, of whom 1489 were randomized, 744 to receive tenecteplase and 745 to receive alteplase

Figure 1. Randomization and Treatment of Patients


1504 Individuals screened for eligibility
15 Excluded[a]
8 Failed the screening[b]
4 Withdrew consent
3 Had no available drug
1489 Randomized
744 Randomized to receive tenecteplase
745 Randomized to receive alteplase
733 Received treatment
11 Did not receive treatment
8 Withdrew consent
2 Had symptom relief
1 Had uncontrolled blood pressure
735 Received treatment
10 Did not receive treatment
4 Withdrew consent
2 Had symptom relief
1 Found to have no cerebral infarction
1 Had acute bleeding diathesis and severe uncontrolled arterial hypertension
1 Had a history of aneurysm
1 Had bleeding
1 Excluded (treated before randomization)[c]
2 Excluded (treated before randomization)
732 Included in full analysis set
733 Included in full analysis set
12 Excluded
6 Assessed in an unblinded manner
2 Could not initiate thrombolytic therapy within 4.5 h of AIS onset
2 Not diagnosed with AIS per inclusion criteria
1 Not diagnosed with AIS per inclusion criteria and assessed in an unblinded manner
1 Did not adhere to study drug intake protocol
7 Excluded
4 Assessed in an unblinded manner
2 Not diagnosed with AIS per inclusion criteria
1 Could not initiate thrombolytic therapy within 4.5 h of AIS onset
720 Included in per-protocol analysis[d]
726 Included in per-protocol analysis[d]

[a]No patients refused to participate in the study.

[b]One patient did not meet the inclusion criteria of thrombolytic therapy being initiated within 4.5 hours of AIS onset; 7 other patients met exclusion criteria related to bleeding risk, infarction, or safety.

[c]Patient was randomly assigned to the tenecteplase group but received alteplase. Thus, 732 patients in the tenecteplase group and 736 patients in the alteplase group were included in the safety set.

[d]The per-protocol analysis excluded those patients who had incorrect drug administration, improper unblinding procedures, did not adhere to study drug intake protocol, or did not meet inclusion criteria.

AIS indicates acute ischemic stroke.

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(**Figure 1**). A total of 1346 patients (90.4%) completed the trial and 78 patients (5.2%) died. The most common reason for prematurely discontinuing from the trial was loss to follow-up (30 patients [2.0%]). The safety set comprised 732 patients in the tenecteplase group and 736 in the alteplase group, after excluding 21 patients who were randomized but not treated due to withdrawal by the patients, among other reasons. Three patients (2 in the alteplase group and 1 in the tenecteplase group) initiated randomization, but completed the randomization procedure after receiving treatment, which met a predefined important protocol deviation and were therefore excluded from the full analysis set. This set comprised 732 patients in the tenecteplase group and 733 patients in the alteplase group, whereas the per-protocol set comprised 720 and 726 patients, respectively.

Baseline demographic and clinical characteristics were generally similar between the treatment groups (**Table 1**). Overall, the median (IQR) age was 66.0 (58.0-73.0) years, the median (IQR) NIHSS score was 6.0 (5.0-9.0), and 446 (30.4%) were female. All but 3 patients received thrombolytic treatment within 4.5 hours after the onset of stroke symptoms; approximately half of the patients (53%) received treatment within a 3-hour time window. A total of 373 patients (25.5%) in both treatment groups had CTA or MRA performed at baseline based on physician assessment. Among these, 130 patients (35%) reported occlusion, mainly in the M1 segment (61/130; Table 1).

Outcomes

Tenecteplase was noninferior to alteplase with regard to the proportion of patients who achieved an excellent functional outcome on day 90 (mRS score of 0 or 1: 72.7% vs 70.3%; adjusted RR, 1.03 [95% CI, 0.97-1.09]; P = .003), the lower bound of which was above the predefined noninferiority margin (0.937; **Table 2**). The null hypothesis for superiority was not rejected since the lower bound of the 95% CI was not above 1 (P = .37). The distribution of mRS scores on day 90 is shown in **Figure 2** and the odds of achieving a better stroke outcome based on the full range of mRS scores are shown in eFigure 1 in Supplement 1. The proportion of patients with an mRS score of 0 to 2 at day 90 was 80.9% for tenecteplase and 79.9% for alteplase (RR, 1.01 [95% CI, 0.96-1.06]; Table 2). The proportion of patients who achieved major neurologic improvement at 24 hours receiving tenecteplase or alteplase was 48.0% and 45.0%, respectively (RR, 1.07 [95% CI, 0.96-1.19]). The number of patients who achieved a Barthel Index score of at least 95 on day 90 was 75.7% for tenecteplase vs 73.9% for alteplase (RR, 1.02 [95% CI, 0.96-1.08]; Table 2). The mean change from baseline in NIHSS score on day 90 was −3.70 for tenecteplase and −3.02 for alteplase (adjusted difference, −0.45 [95% CI, −1.40 to 0.50]; Table 2).

Results of the sensitivity and supplemental analyses of the primary outcome were consistent with those of the primary analysis, with the lower bounds of the 95% CI above the noninferiority margin (eTable 1 in Supplement 1). Tenecteplase was not superior to alteplase since the lower bound of the 95% CI of the adjusted RR was not above 1. In the predefined subgroup analysis, most of the point estimates were greater than 1, favoring tenecteplase (**Figure 3**). The RR of 2.44 was observed in patients older than 80 years and the P value for treatment × age subgroup interaction term was less than .05 (Figure 3). Findings from post hoc subgroup analysis of the primary outcome performed on patients who received CTA or MRA assessment and reported with or without occlusions and the post hoc generalized estimating equations analysis are shown in eTables 1 and 2 in Supplement 1.

Table 1. Patient Baseline Characteristics in the Full Analysis Set

Characteristic	Tenecteplase, No. (%) (n = 732)[a]	Alteplase, No. (%) (n = 733)[a]
Demographics		
Age, median (IQR), y	66 (58-73)	65 (57-73)
>80	47 (6.4)	46 (6.3)
Sex		
Female	215 (29.4)	231 (31.5)
Male	517 (70.6)	502 (68.5)
Comorbidities		
Atrial fibrillation	108 (14.8)	97 (13.2)
Diabetes	199 (27.2)	204 (27.8)
Stroke characteristics		
Baseline NIHSS score, median (IQR)[b]	6 (5.0-8.5)	6 (5.0-9.0)
<6	299 (40.8)	297 (40.5)
6-15	390 (53.3)	393 (53.6)
>15	43 (5.9)	43 (5.9)
<4	79 (10.8)	78 (10.6)
≥4	653 (89.2)	655 (89.4)
Baseline CTA/MRA performed[c]	187 (25.5)	186 (25.4)
Occlusion[d]	66 (35.3)	64 (34.4)
Internal carotid artery	7 (10.6)	9 (14.1)
M1 segment	38 (57.6)	23 (35.9)
M2 segment	8 (12.1)	7 (10.9)
M3 segment	3 (4.5)	2 (3.1)
Tandem	3 (4.5)	4 (6.3)
Anterior cerebral artery	2 (3.0)	2 (3.1)
Posterior cerebral artery	0	5 (7.8)
Other[e]	5 (7.6)	12 (18.8)
Prior stroke in the last 3 mo	14 (1.9)	13 (1.8)
Time to study drug administration, h[f]		
≤3	402 (54.9)	375 (51.2)
>3	330 (45.1)	358 (48.8)
Thrombectomy performed	61 (8.3)	54 (7.4)

Abbreviations: CTA, computed tomography angiography; MRA, magnetic resonance angiography; NIHSS, National Institutes of Health Stroke Scale.

[a] Unless otherwise indicated.

[b] NIHSS is a standardized neurologic examination comprising 15 questions covering 11 specific functions scored on a scale of 0 to 4, where 0 indicates normal functioning and 4 indicates complete impairment; a score of 42 indicates death.

[c] Among those with baseline CTA/MRA performed, 66 (17.7%) underwent thrombectomy procedures (tenecteplase, 20.3%; alteplase, 15.1%).

[d] Percentages of occlusion type calculated using total number of patients with occlusions as denominator.

[e] Other occlusions included vertebral artery, basilar artery, and other distal arteries.

[f] Since onset of stroke symptoms by class.

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Table 2. Patient Outcomes

	Tenecteplase	Alteplase	RR (95% CI)[a]	RD (95% CI)[a]
Efficacy (full analysis set), No.[b]	732	733		
Primary efficacy outcome, No. (%)				
Patients with mRS score 0-1 on day 90[c,d]	532 (72.7)	515 (70.3)	1.03 (0.97 to 1.09)[e]	2.12 (−2.17 to 6.40)
Secondary efficacy end points				
Major neurologic improvement at 24 h, No. (%)[f,g]	341 (48.0)	322 (45.0)	1.07 (0.96 to 1.19)	2.78 (-2.34 to 7.89)
mRS score 0-2 on day 90, No. (%)[d]	592 (80.9)	586 (79.9)	1.01 (0.96 to 1.06)	0.74 (-3.02 to 4.50)
Change in NIHSS score from baseline to day 90, mean (SD)[g,h]	−3.70 (8.83)	−3.02 (9.68)		−0.45 (−1.40 to 0.50)
Distribution of mRS score on day 90[i]			1.04 (0.93 to 1.17)	
Barthel Index score of at least 95 on day 90, No. (%)[d,j]	529 (75.7)	523 (73.9)	1.02 (0.96 to 1.08)	1.53 (-2.63 to 5.68)
Safety (safety set), No. (%)[k]	732	736		
sICH while receiving treatment[l]	9 (1.2)	9 (1.2)	1.01 (0.37 to 2.70)	0.00 (-1.25 to 1.24)
All-cause mortality within 90 d[m]	34 (4.6)	43 (5.8)	0.80 (0.51 to 1.23)	-1.20 (-3.48 to 1.08)
mRS of 5 or 6 on day 90[d,n]	50 (6.8)	57 (7.8)	0.92 (0.66 to 1.29)	-0.79 (-3.27 to 1.69)

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RD, risk difference; RR, risk ratio; sICH, symptomatic intracerebral hemorrhage.

[a] Unless otherwise indicated.

[b] Three patients (2 in the alteplase group and 1 in the tenecteplase group) initiated randomization, but completed the randomization procedure after receiving treatment, which met a predefined important protocol deviation, and were therefore excluded from the full analysis set.

[c] The mRS is a 6-point scale used to measure the degree of global disability, with scores ranging from 0 (no symptoms) to 6 (death), where 1 indicates no significant disability and 5 indicates severe disability. An mRS of 0 or 1 is considered excellent.

[d] Modified Poisson model with treatment as main effect and baseline NIHSS score, age, and time to study drug administration as continuous covariates.

[e] *P* value for noninferiority testing was .003; *P* value for superiority testing was .37.

[f] NIHSS score of 0 or at least a 4-point improvement from baseline.

[g] Log-binomial regression including treatment as a categorical effect and baseline NIHSS score, age, and time to study drug administration as continuous covariates; the observed cases approach was used.

[h] Restricted maximum likelihood–based mixed-model for repeated measures model including baseline NIHSS score, age, and time to study drug administration as linear covariates, treatment as a fixed effect, and treatment × visit and baseline NIHSS score × visit interactions; results presented as mean (SD) for both groups and adjusted mean difference (95% CI) for tenecteplase vs alteplase.

[i] Ordinal logistic regression model including treatment as main effect and baseline NIHSS score, age, and time to study drug administration as continuous covariates; stated as an odds ratio.

[j] The Barthel Index, a measure of functional independence, is assessed using 10 items, each item scores 0 to 1, 0 to 2, or 0 to 3, depending on the function. Total scores range from 0 to 100, with lower scores indicating less independence.

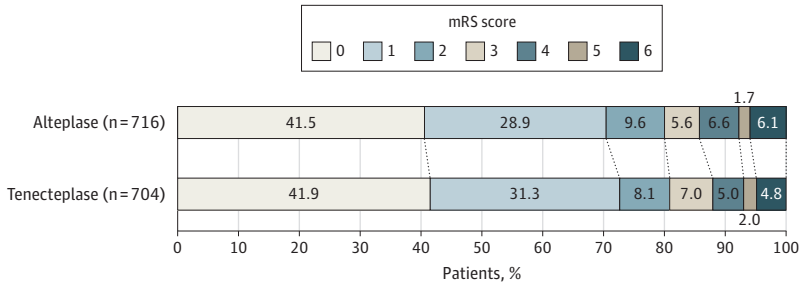
[k] One patient was randomly assigned to the tenecteplase group but received alteplase.

[l] Analyzed based on the European Cooperative Acute Stroke Study III definition of symptomatic intracerebral hemorrhage measured up to 36 hours after stroke onset, using the Suissa-Shuster test with no imputation for missing data; 95% CI calculated using the Chan-Zhang method.

[m] χ^2 test with no imputation for missing data; 95% CI calculated using the Wald method.

[n] Analyzed in the full analysis set.

Figure 2. Distribution of Modified Rankin Scale (mRS) Scores on Day 90 in the Full Analysis Set



Data were analyzed based on observed cases. mRS score on day 90 was missing for 3.8% of the tenecteplase group (N = 732) and 2.3% of the alteplase group (N = 733). The sum of percentages may be more than 100 due to rounding. The mRS is a 6-point disability scale (0 = no symptoms; 1 = no significant disability; 2 = slight disability; 3 = moderate disability; 4 = moderately severe disability; 5 = severe disability; 6 = death).

The adjudicated sICH per the ECASS III definition occurred in 9 patients (1.2%) in both the tenecteplase and alteplase groups (RR, 1.01 [95% CI, 0.37-2.70]; Table 2), which resulted in the deaths of 3 patients receiving tenecteplase and 5 patients receiving alteplase. Adjudicated sICH events per the SITS-MOST definition were 1.4% for tenecteplase and 1.1% for alteplase and per ECASS II definition were 2.6% and 3.0%, respectively (eTable 4 in Supplement 1). Intracranial hemorrhage, identified via cerebral imaging, occurred in 8.1% and 8.6% of patients in the tenecteplase and alteplase groups, respectively (eTable 5 in Supplement 1). Further details on adjudicated sICH are available in eTable 6 in Supplement 1. Systemic bleeding (eTable 7 in Supplement 1) and angioedema (eTable 8 in Supplement 1) were collected through adverse event reporting. None of the cases of systemic bleeding were fatal.

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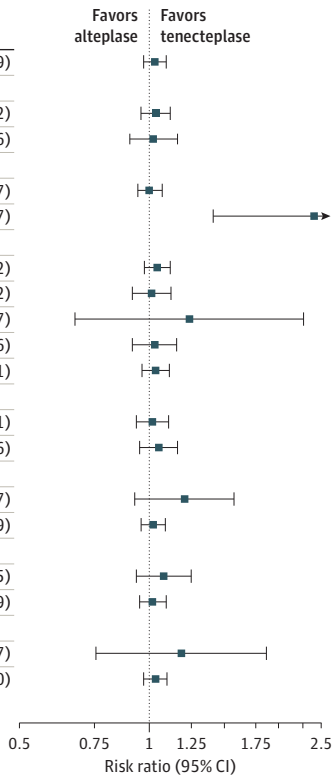
Figure 3. Proportions of Patients Achieving a Modified Rankin Scale Score of 0 or 1 on Day 90 (Primary Outcome) in Prespecified Subgroups

	No./total No. (%)		Risk ratio (95% CI)
	Tenecteplase	Alteplase	
Overall	532/732 (72.7)	515/733 (70.3)	1.03 (0.97-1.09)
Sex			
Male	382/517 (73.9)	358/502 (71.3)	1.04 (0.96-1.12)
Female	150/215 (69.8)	157/231 (68.0)	1.02 (0.90-1.16)
Age, y			
≤80	501/685 (73.1)	503/687 (73.2)	1.00 (0.94-1.07)
>80	31/47 (66.0)	12/46 (26.1)	2.44 (1.42-4.17)
Baseline NIHSS score			
<6	258/299 (86.3)	246/297 (82.8)	1.04 (0.97-1.12)
6-15	258/390 (66.2)	257/393 (65.4)	1.01 (0.91-1.12)
>15	16/43 (37.2)	13/43 (30.2)	1.24 (0.67-2.27)
<4	70/79 (88.6)	68/78 (87.2)	1.03 (0.91-1.16)
≥4	462/653 (70.8)	448/655 (68.4)	1.03 (0.96-1.11)
Time to study drug administration, h[a]			
≤3	298/402 (74.1)	274/375 (73.1)	1.02 (0.93-1.11)
>3	234/330 (70.9)	242/358 (67.6)	1.05 (0.95-1.16)
Atrial fibrillation			
Yes	62/108 (57.4)	46/97 (47.4)	1.21 (0.92-1.57)
No	470/624 (75.3)	469/636 (73.7)	1.02 (0.96-1.09)
Diabetes			
Yes	134/199 (67.3)	128/204 (62.7)	1.08 (0.93-1.25)
No	398/533 (74.7)	388/529 (73.3)	1.02 (0.95-1.09)
Thrombectomy performed			
Yes	27/61 (44.3)	20/54 (37.0)	1.18 (0.75-1.87)
No	505/671 (75.3)	495/679 (72.9)	1.03 (0.97-1.10)



A log-binomial regression model was fitted to each subgroup separately by modeling the primary outcome with treatment, subgroup, and treatment-by-subgroup interaction terms. Only the *P* value for treatment × age interaction was less than .05. The multiple imputation approach was used for missing data. NIHSS indicates National Institutes of Health Stroke Scale.

[a]From onset of stroke symptoms.

Mortality within 90 days for patients receiving tenecteplase and patients receiving alteplase was 4.6% vs 5.8%, respectively (RR, 0.80 [95% CI, 0.51-1.23]), and the proportion of patients with an mRS score of 5 or 6 on day 90 was 6.8% vs 7.8%, respectively (RR, 0.92 [95% CI, 0.66-1.29]) (Table 2).

Discussion

This trial found that in patients with AIS eligible for intravenous thrombolysis within 4.5 hours after stroke onset, tenecteplase 0.25 mg/kg was noninferior to alteplase for achieving an mRS score of 0 or 1 at day 90.

Results of this study in Chinese patients with AIS were consistent with those of investigator-initiated trials, including the AcT trial, a phase 3, pragmatic, registry-linked, randomized controlled study conducted in Canada,[15] and ATTEST-2, a prospective, randomized, controlled, parallel-group trial completed in the UK in 2023.[27] In the ORIGINAL study, the adjusted risk difference between tenecteplase and alteplase for the primary outcome was 2.12% (95% CI, −2.17 to 6.40), which is consistent with that observed in the AcT (unadjusted risk difference, 2.1% [95% CI, −2.6 to 6.9]) and ATTEST-2 (risk difference, 1.99% [95% CI, −2.77 to 6.75]) studies.[15,27] The 2023 TRACE-2 study in China demonstrated the noninferiority of tenecteplase (using a locally manufactured version from CSPC Pharmaceutical Group) to alteplase in Chinese patients with AIS eligible for standard intravenous thrombolysis, but ineligible for or who refused endovascular thrombectomy. Although baseline patient characteristics were similar between TRACE-2 and this study, TRACE-2 excluded patients eligible for endovascular thrombectomy and those with an NIHSS score at or below 4.[17]

The study observed that proportions of patients who achieved an mRS score of 0 or 1 at day 90 in both treatment groups were greater than those in the AcT trial (tenecteplase, 36.9%; alteplase, 34.8%). This was associated with the different baseline severity between 2 studies: the patient population in the AcT trial was older and had a higher mean NIHSS score (9-10) than in this study.[15] Almost one-third of the patients in the AcT trial had an NIHSS score greater than 15 vs 5.9% in this study. Both age and NIHSS score can strongly predict the likelihood of a patient's recovery after AIS[28]; in particular, those with severe impairment (NIHSS score >15) had a less than 20% chance of achieving an excellent outcome.[29] Nonetheless, the AcT study demonstrated that the noninferiority finding is consistent among those with severe stroke and those with more moderate (NIHSS score 8-15) and mild (NIHSS score <8) strokes.[15]

This study enrolled a population of patients that reflects those in real-world practice who are eligible for intravenous thrombolysis. This was consistent with the label for alteplase, which includes recommendations for thrombolysis in patients with mild AIS with functional disability and in those for whom endovascular thrombectomy was planned.[6,30] The primary outcome was consistent across prespecified subgroups, including

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baseline NIHSS score, age, time to drug administration, sex, comorbidities, and thrombectomy performed. Similar to TRACE-2,[17] this study showed that tenecteplase was associated with excellent 90-day functional outcomes in patients aged 80 years or older, although the sample size was too small to draw meaningful conclusions. Results from recently completed phase 3 trials, including ATTEST-2 (NCT02814409) and TASTE (ACTRN12613000243718) will further shed light on the utility of tenecteplase 0.25 mg/kg in various patient populations.[27,31]

This study had centralized adjudication of sICH events by an end point adjudication committee and regular review of safety data by a data monitoring committee. sICH events were identified per ECASS III, SITS-MOST, and ECASS II definitions.[20,32,33] The incidence of adjudicated sICH events, regardless of definition, and any intracranial hemorrhage were similar between both treatment groups. The lower baseline stroke severity in this trial also resulted in lower sICH rates in this trial compared with AcT.[15] The rates of mortality and mRS scores of 5 to 6 at 90 days did not differ significantly between groups. Although the 90-day mortality rate for tenecteplase was lower in this trial compared with the AcT trial, it was similar to that reported in TRACE-2 (15.3% for tenecteplase in AcT; 7% for tenecteplase in TRACE-2), likely due to similar baseline characteristics in this study and TRACE-2.[15,17]

The rate of patients who underwent thrombectomy in this study was also limited (<10% of overall patients), lower than the rate reported in the AcT trial.[15] However, the rate was higher when explored specifically in patients who received baseline CTA and/or MRA procedures in this study (tenecteplase, 20.3%; alteplase, 15.1%), which suggests that in addition to an overall less severe stroke severity compared with the AcT trial, thrombectomy could have been limited by the availability of advanced imaging facilities or endovascular therapy at the respective study sites. Additionally, females represented only about 30% of the total study population. Participation of females in stroke clinical trials remains consistently low in both local (China Alteplase 3-4.5h trial[20] and TRACE-II,[17] 20%-32%) and international trials (ECASS-III, 20%[20]; WAKE-UP, 35%[34]). Similarly, males outnumber females in real-world treatment settings according to local large stroke registries (31.7%-35.6% in BOSC[35] and CNSR-III[36]).

This study strengthens the understanding of tenecteplase in AIS by further building on the results from previous trials, including TAAIS,[12] TNK-S2B, ATTEST,[13] NOR-TEST,[19] and EXTEND-IA TNK[14], as well as the large clinical trial AcT.[15] Together, these studies have provided evidence on the use of tenecteplase, including the optimal dosing and use in clinical subgroups, such as patients with large vessel occlusion (LVO). The overall treatment effect in this study of Chinese patients can be expected to be similar to other populations beyond China, given the comparability of the current result with existing studies, which comprise non-Asian populations across various stroke severities.[15,17,20,32,33]

Limitations

This study has limitations. First, the study employed an open-label design, which may have influenced post-procedural patient care, even though end point assessment was performed by a blinded reviewer. Second, the subgroup of patients with LVO in the post hoc analysis only represented those who had suspected LVO and had completed baseline imaging assessment (CTA/MRA), the availability of which was variable at study sites. Third, the study did not record stroke mimic data; stroke mimics were inevitably included in this trial and can be considered as part of routine acute stroke care. The probability of stroke mimics may be higher in patients with AIS aged 60 years or younger, females, or patients with a lower NIHSS score at admission.[19]

Conclusions

Tenecteplase was noninferior to alteplase with respect to excellent functional outcomes (mRS score of 0 or 1) at 90 days in patients with AIS within 4.5 hours of symptom onset. Findings from this study provide evidence to support the use of tenecteplase as a suitable alternative to alteplase in these patients.

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